Attorney Docket No.: 5739.200-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
FILING UNDER 37 C.F.R. 1.53(b)

Box Patent Application
Assistant Commissioner for Patents
Washington, DC 20231

Express Mail Label No. EL021370267US
Date of Deposit November 30, 1999
Sir:

This is a request for filing an application under 37 C.F.R. 1.53(b) of

Applicant(s): Weibel et al.

Title: New Pharmaceutical Composition And The Process For Its Preparation

16 pages of specification 0 sheets of drawings

3 sheets of Declaration and Power of Attorney

[x] The filing fee is calculated as follows:

Basic Fee:	$760.00
Total Claims: 19 - 20 = 0 x 18 =	$0
Independent Claims: 2 - 3 = 0 x 78 =	$0
Total Fee:	$760.00

Priority of Danish application no. PA 1998 01580 filed on December 1, 1998 is claimed under 35 U.S.C. 119. A certified copy is submitted herewith.

Priority of U.S. provisional application no. 60/112,248 filed on December 14, 1998 is claimed under 35 U.S.C. 119.

Address all future communications to Steve T. Zelson, Esq., Novo Nordisk of North America, Inc., 405 Lexington Avenue, Suite 6400, New York, NY 10174-6401.

Please charge the required fee, estimated to be $760, to Novo Nordisk of North America, Inc., Deposit Account No. 14-1447. A duplicate of this sheet is enclosed.

Respectfully submitted,

Date: November 30, 1999

Elias J. Lambiris, Reg. No. 33,728
Novo Nordisk of North America, Inc.
405 Lexington Avenue, Suite 6400
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Attorney Docket No.: 5739.200-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

EXPRESS MAIL CERTIFICATE

Box Patent Application
Assistant Commissioner for Patents
Washington, DC 20231

Re: U.S. Patent Application for
Title: New Pharmaceutical Composition And The Process For Its Preparation
Applicants: Weibel et al.

Sir:

Express Mail Label No. EL021370267US

Date of Deposit : November 30, 1999

I hereby certify that the following attached paper(s) or fee

1. Filing Under 37 C.F.R. 1.53(b) (in duplicate)
2. Patent Application
3. Unexecuted Combined Declaration and Power of Attorney
4. Preliminary Amendment
5. Certified Copy of Priority Application

are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231.

Gina Maldonado
(Name of person mailing paper(s) or fee)

(Signature of person mailing paper(s) or fee)

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Attorney Docket No.: 5739.200-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Weibel et al.

Application No.: To be assigned Group Art Unit: To be assigned

Filed: November 30, 1999 Examiner: To be assigned

For: New Pharmaceutical Composition And The Process For Its Preparation

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Before the above-captioned application is taken up for examination, entry of the following amendment is respectfully requested:

IN THE SPECIFICATION:

At page 1, after the title, insert

--CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. 119 of Danish application PA 1998 01580 filed December 1, 1998 and of U.S. Provisional application 60/112,248 filed December 14, 1998, the contents of which are fully incorporated herein by reference.--

IN THE CLAIMS:

Please cancel claims 20-27 without prejudice or disclaimer.

Please amend claim 3 as follows:

At line 1, delete "or 2".

Please amend claim 4 as follows:

At line 1, delete "or 2"

At line 3, delete "a" and insert --the--

At line 3, delete "according to claim 3".

Please amend claim 5 as follows:

At line 1, delete "or 4".

Please amend claim 8 as follows:

At line 1, delete "or 7".

Please amend claim 9 as follows:

At line 1, delete "or 7".

Please amend claim 10 as follows:

At line 1, delete "or 7".

Please amend claim 11 as follows:

At line 1, delete "or 7".

Please amend claim 12 as follows:

At line 1, delete "or 7".

Please amend claim 13 as follows:

At line 1, delete "or 7".

Please amend claim 14 as follows:

At line 1, delete "or 7".

Please amend claim 15 as follows:

At line 1, delete "or 7".

Please amend claim 16 as follows:

At line 1, delete ",2, 6 or 7".

Please amend claim 17 as follows:

At line 1, delete "or 7".

Please amend claim 18 as follows:

At line 1, delete "or 7"

At line 3, delete "a" and insert --the--

At line 3, delete "according to claim 17".

Please amend claim 19 as follows:

At line 1, delete "or 18".

REMARKS

This amendment is submitted to correct improper multiple dependent claims. Since only dependencies are altered, there is no new matter added, and entry of the amendment is respectfully requested.

Respectfully submitted,

Date: November 30, 1999

Elias J. Lambiris, Reg. No. 33,728
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New pharmaceutical composition and the process for its preparation

The subject-matter of the present invention is a new pharmaceutical composition containing 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione as active ingredient and the process for its preparation.

5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione and pharmaceutically acceptable salts thereof has been found useful in the treatment of type 2 diabetes acting as a insulin sensitizer as disclosed in PCT Publication WO 97/41097.

The active ingredient is present as the base or as a pharmaceutically acceptable salt, preferably as the potassium salt.

Various solutions have been proposed for the preparation of medications based on 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione.

The aim of the present invention is to provide a new composition intended for the preparation of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione with improved stability, in particular solid dosage forms thereof.

It has been found in fact that 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quina-zolinyl]meth-oxy]-phenyl-methyl]thiadiazolidine-2,4-dione and its pharmaceutically acceptable salts may decompose in the presence of and in contact with water. Further it has been observed that decomposing may occur in the presence of oxygen.

Thus, from a first aspect, the subject-matter of the present invention is a pharmaceutical composition intended for the preparation of dosage forms and in particular solid dosage forms containing an efficacious quantity of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione or of one of its pharmaceutically acceptable salts as active ingredient.

The present invention is based on the surprising discovery of the fact that the stability of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, or of one of its pharmaceutically acceptable salts, can be considerably improved in preparations containing 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione or of its pharmaceutically acceptable salts and antioxidant agent if the product is composed of excipients which do not contain water.

Pharmaceutically acceptable salts forming part of this invention include salts such as alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline and the like, ammonium or substituted ammonium salts, aluminium salts. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulplionates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like.

5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, together with a conventional adjuvant, antioxidant carrier, or diluent, and if desired a pharmaceutically acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or oral powders to be diluted immediately before use filled with the same, all for oral use, in the form of suppositories for rectal administration; or as pessaries for vaginal use; or in the form of sterile injectable powders for parenteral, transdermal, nasal, pulmonary and ocular use.

Within the framework of the present description and of the claims, by powders is meant any mixture of components, granulated or not, intended to be placed in solution and/or in suspension in water, or again to be ingested directly or by any other appropriate means as for example in a mixture with a food product.

In accordance with a particular characteristic of the invention, the manufacture of tablets are carried out as a direct compression.

In accordance with another particular characteristic, this composition also contains pharmaceutically acceptable excipients.

In accordance with a particular characteristic of the invention, the antioxidant agent cited above is selected from among α-tocopherol, γ-tocopherol, δ-tocopherol, extracts of natural origin rich in tocopherol, L-ascorbic acid and its sodium or calcium salts, ascorbyl palmitate, propyl gallate (PG), octyl gallate, dodecyl gallate, butylated hydroxy anisole (BHA) and butylated hydroxy toluene (BHT).

In accordance with a currently preferred embodiment, the antioxidant agent will be α-tocopherol.

In accordance with another particular characteristic of the invention, the diluent is lactose and/or cellulose microcrystalline, magnesium stearate, talc.

However, any other pharmaceutically acceptable diluents could be used if the diluents has a low water content.

The quantities of diluents can be easily determined by a person skilled in the art and depend of course on the final pharmaceutical form required.

Generally speaking, a composition which complies with the present invention and which are intended for the preparation of tablets, may contain, expressed in parts by weight per 100 parts of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, or of one of its pharmaceutically acceptable salts:

between 100 and 400,000 parts by weight of anhydrous lactose;
between 1 and 100 parts by weight of an antioxidant;
between 50 and 500 parts by weight of pregelatinized starch;
between 1000 and 10,000 parts by weight of microcrystalline cellulose;
between 10 and 500 parts by weight of crospovidone;
between 10 and 500 parts by weight of silicon dioxide;
between 10 and 500 parts by weight of hydrogenated vegetable oil;

between 10 and 500 parts by weight of magnesium stearate;
between 10 and 500 parts by weight of hydroxypropyl methylcellulose;
between 10 and 500 parts by weight of hydroxypropyl cellulose;
between 1000 and 10,000 parts by weight of Mannitol;
between 10 and 500 parts by weight of stearic acid;
between 10 and 500 parts by weight of Titanium Dioxide;

According to a preferred embodiment of the invention the water content of the excipients is very low. More specifically the water content in the diluents is very low in order to minimize the water content of the pharmaceutical composition. Lactose is used in its anhydrous form.

Furthermore, all excipients may be applied in a dry form.

In accordance with a second aspect, the subject-matter of the present invention is a pharmaceutical preparation, in the form of tablet or powder, characterised in that it contains a composition as defined previously associated if required with at least one customary additive selected from among the sweeteners, flavouring agents, colours and lubricants.

The choice of these additives and their quantity can easily be determined by a person skilled in the art.

Another manufacturing process for pharmaceutical compositions according to the invention is mixing of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, one or more antioxidants and other pharmaceutical excipients followed by melt granulation in a high shear mixer. Hydrogenated, vegetable oil, waxes or other low temperature melting binders can be used. The granules can be filled into capsules, compressed into tablets or used in other pharmaceutical dosage forms.

More preferably the manufacturing process applied is direct compression of tablets, wherein 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, one or more antioxidants and other excipients suitable for direct compression are mixed followed by tabletting.

Yet, another preferred embodiment of the manufacturing process is wet granulation, where granules are obtained by wet massing of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, together with one or more anti-oxidants and other excipients.

It is assumed that the contact time with water have to be very short.

The most preferred process comprises the direct compression whereby 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione is kept at conditions of low water vapour pressure.

A sweetener may be a natural sugar such as sorbitol or a synthetic product such as saccharine or aspartame.

When the antioxidant selected is ascorbylpalmitat, propylgallat, which is a powder, it can be advantageous to mix it in an appropriate excipient such as α-tocopherol succinat, lactose or cellulose micrycrystalline.

The present invention will further be illustrated with the following non-exhaustive examples.

In Example 1 through 4 the tablets were prepared according to the following procedure:

The active ingredient is mixed with cellulose microcrystalline in a drum mixer for 10 minutes.
Lactose is added and the mixing continued for further two minutes.
The lubricants are added and the mixing continued for further two minutes.

EXAMPLE 1

25 mg 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt Tablets 807227

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt, 003/97	9%
Cellulose Microcrystallline	20%
Lactose	66%

Magnesium Stearate	0.5%
Talc	4.5%

EXAMPLE 2

50 mg 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt tablets 807237

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt, 003/97	18%
Cellulose Microcrystalline	20%
Mannitol	57%
Magnesium Stearate	0.5%
Talc	4.5%

EXAMPLE 3

50 mg 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt Tablets 731725

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt	18%
Lactose	81.5%
Magnesium stearate	0.5%

EXAMPLE 4

0.25 mg 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt Tablets 728625

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt	0.09%
Mannitol	98%
Magnesium stearate	2%

EXAMPLE 5

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt	0.09%
Hydrogenated vegetable oil	6.25%
Talc	5%
α-tocopherol	50% of 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt
Lactose DCL21/Mannitol	Up to 200 g

The granulate is manufactured in a Baker Perkins 1 L high-shear mixer - using a water bath of 70°C. The mixing is carried out at 3000 RPM, chopper 6000 RPM and the granulation is performed at approx. 70°C. The hot granulate is sieved through sieve 1.25 μm, and the cold granulate through sieve 1000 μm. The glidant is added with a card for 2 min. The tablets are manufactured using a Diaf tablet machine with 9 mm punch.

In order to protect against light and improve the appearance of the tablets, the tablets are film-coated.

The tablets were coated with the following film-coating composition where an amount of coating material of 5 mg/cm^2 were chosen as being satisfactory with respect to stability of the tablets:

Methylhydroxypropylcellulose, Ph. Eur.....	~ 4.34 mg/tablet
Titanium Dioxide, Ph. Eur.....	~ 1.73 -
Purified Water, Ph. Eur.....	q.s. -

Talc, Ph. Eur. (Added as polishing agent at the end of the film-coating process (0.5 % w/w of tablet core). Absorbed amount is not quantified.

EXAMPLE 6

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt	0.09%

Povidone	7.5%
Hydroxypropylmethyl cellulose	1.5%
Croscarmelose sodium	1.56%
Talc	1.1%
Magnesium stearate	0.5%
Lactose 300 mesh	up to 200 g

The granulate is manufactured by Baker Perkins 1 L intensive mixer. Dry mixing were carried out at 500 RPM, chopper 1500 RPM and granulation 1000 RPM and 2000 RPM. The wet granulate is sieved through sieve 1.25 μm and the dry granulate through sieve 1000 μm. The glidant is admixed with a card for 2 min. The tablets are manufactured by Diaf tablet machine with 9 mm punch.

EXAMPLE 7

Composition:	Oral Powder, 1 mg/ml, 100 ml
5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione potassium salt	0.1096 g
Mannitol	2.5 g
Hydroxypropyl-β-cyclodextrin	10 g

To be diluted with 92 mL water before use.

EXAMPLE 8

Composition:	Oral Powder, 10 mg/ml, 100 ml
5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione potassium salt	1.096 g
Mannitol	2.5 g
Hydroxypropyl-β-cyclodextrin	10 g
Sodium Carbonate, anhydrous,	

Na_2CO_3	15 mg

To be diluted with 92 mL water before use.

CLAIMS

1. Pharmaceutical composition comprising
5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof,
and optionally a pharmaceutically acceptable carrier.

2. A composition according to claim 1 in the form of a tablet, a powder or a capsule.

3. A process for the preparation of a composition according to claim 1 or 2 which comprises the step of forming a mixture of:
5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof,
and one or more pharmaceutically acceptable carriers.

4. A process for the preparation of a composition according to claim 1 or 2 which comprises the following steps:
forming a mixture according to claim 3,
and direct compression of the mixture with excipients of a low water content.

5. A process according to claim 3 or 4 characterized in that the steps are carried out at low water vapour pressure and low oxygen pressure.

6. A pharmaceutical composition comprising
5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof,
and pharmaceutically acceptable excipients with low water content and an antioxidant.

7. The pharmaceutical composition according to claim 6 in the form of a tablet, a powder or a capsule.

8. The pharmaceutical composition according to claim 6 or 7 containing, expressed in parts by weight per 100 parts of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, or of one of its pharmaceutically acceptable salts and be-

tween 1 and 100 parts by weight of an antioxidant and the pharmaceutically acceptable excipients selected among the following:

between 100 and 400,000 parts by weight of anhydrous lactose,

between 1 and 100 parts by weight of an antioxidant,

between 50 and 500 parts by weight of pregelatinized starch,

between 1000 and 10,000 parts by weight of microcrystalline cellulose,

between 10 and 500 parts by weight of crospovidone,

between 10 and 500 parts by weight of silicon dioxide,

between 10 and 500 parts by weight of hydrogenated vegetable oil,

between 10 and 500 parts by weight of magnesium stearate,

between 10 and 500 parts by weight of hydroxypropyl methylcellulose,

between 10 and 500 parts by weight of hydroxypropyl cellulose,

between 1000 and 10,000 parts by weight of Mannitol,

between 10 and 500 parts by weight of stearic acid,

between 10 and 500 parts by weight of Titanium Dioxide.

9. The pharmaceutical composition according to claim 6 or 7 wherein the pharmaceutically acceptable excipients are selected among from the following:

between 100 and 400,000 parts by weight of anhydrous lactose,

between 50 and 500 parts by weight of pregelatinized starch,

between 1000 and 10,000 parts by weight of microcrystalline cellulose,

between 10 and 500 parts by weight of crospovidone,

between 10 and 500 parts by weight of silicon dioxide,

between 10 and 500 parts by weight of hydrogenated vegetable oil,

between 10 and 500 parts by weight of magnesium stearate,

between 10 and 500 parts by weight of hydroxypropyl methylcellulose,

between 10 and 500 parts by weight of hydroxypropyl cellulose,

between 1000 and 10,000 parts by weight of Mannitol,

between 10 and 500 parts by weight of stearic acid,

between 10 and 500 parts by weight of Titanium Dioxide,

expressed in parts by weight per 100 parts of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, or of one of its pharmaceutically acceptable salts.

10. The pharmaceutical composition according to claim 6 or 7 wherein the pharmaceutically acceptable excipients are selected from the following:
lactose and/or cellulose microcrystalline, magnesium stearate or talc.

11. The pharmaceutical composition according to claim 6 or 7 wherein the pharmaceutically acceptable excipients have a low water content.

12. The pharmaceutical composition according to claim 6 or 7 wherein the pharmaceutically acceptable excipients have a very low water content.

13. The pharmaceutical composition according to claim 6 or 7 wherein the pharmaceutically acceptable excipients are in a dry form.

14. The pharmaceutical composition according to claim 6 or 7 wherein the antioxidant is selected from the following:
α-tocopherol, γ-tocopherol, δ-tocopherol, extracts of natural origin rich in tocopherol, L-ascorbic acid and its sodium or calcium salts, ascorbyl palmitate, propyl gallate (PG), octyl gallate, dodecyl gallate, butylated hydroxy anisole (BHA) or butylated hydroxy toluene (BHT).

15. The pharmaceutical composition according to claim 6 or 7 wherein the antioxidant is α-tocopherol.

16. The pharmaceutical composition according to claim 1,2, 6 or 7 associated with at least one customary additive selected from among the sweeteners, flavouring agents, colours and lubricants.

17. A process for the preparation of a composition according to claim 6 or 7 which comprises the step of forming a mixture of:
5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof,
and one or more pharmaceutically acceptable excipients and an antioxidant.

18. A process for the preparation of a composition according to claim 6 or 7 which comprises the following steps:

forming a mixture according to claim 17, and direct compression of the mixture.

19. A process according to claim 17 or 18 characterized in that the steps are carried out at low water vapour pressure and low oxygen pressure.

20. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt	9%
Cellulose Microcrystallline	20%
Lactose	66%
Magnesium Stearate	0.5%
Talc	4.5%.

21. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt	18%
Cellulose Microcrystalline	20%
Mannitol	57%
Magnesium Stearate	0.5%
Talc	4.5%.

22. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt	18%
Lactose	81.5%
Magnesium stearate	0.5%.

23. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt	0.09%

Mannitol	98%
Magnesium stearate	2%.

24. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt	0.09%
Hydrogenated vegetable oil	6.25%
Talc	5%
α-tocopherol	50% of 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt
Lactose DCL21/Mannitol	Up to 200 g.

25. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt	0.09%
Povidone	7.5%
Hydroxypropylmethyl cellulose	1.5%
Croscarmelose sodium	1.56%
Talc	1.1%
Magnesium stearate	0.5%
Lactose 300 mesh	up to 200 g.

26. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt	0.1096 g
Mannitol	2.5 g
Hydroxypropyl-β-cyclodextrin	10 g

and diluted with 92 mL water before use.

27. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt	1.096 g
Mannitol	2.5 g
Hydroxypropyl-β-cyclodextrin	10 g
Sodium Carbonate, anhydrous, Na_2CO_3	15 mg

and diluted with 92 mL water before use.

ABSTRACT

The present invention provides a new stable pharmaceutical composition containing 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione as active ingredient.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)	**Attorney's Docket Number:** **5739.200-US**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

New Pharmaceutical Composition And The Process For Its Preparation

The specification of which (check only one item below):
[ ] is attached hereto
[**X**] was filed as United States application

Application No. To Be Assigned

on November 30, 1999
and was amended
on

[ ] was filed as PCT international application
Number
on
and was amended under PCT Article 19
on

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by an amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim priority benefits under Title 35, United States Code, §119 of any provisional or foreign application(s) for patent or inventor's certificate or of any PCT international applications(s) for patent or inventor's certificate or of any PCT international applications(s) designating at least one country other htan the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR U.S. PROVISIONAL/FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicated "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
DK	PA 1998 01580	1 December 1998	[x] YES [ ] NO
US	60/112,248	14 December 1998	[x] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

Attorney's Docket Number: **5739.200-US**

I hereby claim the benefit under Title 35, United States Code '120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this applications is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, '112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, '1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U S APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U S.C 120

U S APPLICATIONS		STATUS (Check one)		
U.S. APPLICATION NUMBER	U.S FILING DATE	Patented	Pending	Abandoned

PCT APPLICATIONS DESIGNATING THE U.S

APPLICATION NO.	FILING DATE	US SERIAL NUMBERS ASSIGNED (if any)			

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith Steve T Zelson Elias J. Lambiris Valeta A Gregg Carol E Rozek Robert L Starnes Reza Green, Reg. No 30,335 Reg No 33,728 Reg. No. 35,127 Reg. No 36,993 Reg No. 41,324 Reg No. 38,475

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COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)				**Attorney's Docket Number: 5739.200-US**
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	Residence & Citizenship	City	State or Foreign Country	Country of Citizenship
	Post Office Address	Post Office Address	City	State & Zip Code/Country

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon

Signature of Inventor 1	Signature of Inventor 2	Signature of Inventor 3
Date	Date	Date
Signature of Inventor 4	Signature of Inventor 5	Signature of Inventor 6
Date	Date	Date
Signature of Inventor 7	Signature of Inventor 8	Signature of Inventor 9
Date	Date	Date